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Family:

PDF	Publication	Pub. Date	Filed	Title
	WO9609056A1	1996-03-28	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
	US5916593	1999-06-29	1997-09-16	Process of making dosage units by w
☑	RU2166936C2	2001-05-20	1995-09-19	METHOD OF PREPARING DOSING WET GRANULATION METHOD
☑	PT0782449T	2003-07-31	1995-09-19	PROCESSO DE FABRICO DE UNID DOSAGEM POR GRANULACAO HU
☑	PL0319373A1	1997-08-04	1995-09-19	METHOD OF PRODUCING SINGLE WET GRANULATION
☑	PL0181406B1	2001-07-31	1995-09-19	METHOD OF PRODUCING SINGLE WET GRANULATION
☑	NZ0293606A	1998-06-26	1995-09-19	PREPARATION OF PHARMACEUT UNITS OF A STEROIDAL PROGEST MIXING WITH WATER AND GRANU SOLUTION
☑	NO0971361A0	1997-03-21	1997-03-21	FREMGANGSMAATE FOR FREMST DOSERINGSENHETER VED VAATGRANULERING
☑	NO0971361A	1997-05-21	1997-03-21	FREMGANGSMAATE FOR FREMST DOSERINGSENHETER VED VAATGRANULERING
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☑	NO0311492B1	2001-12-03	1997-03-21	DOSERINGSENHETER OMFATTEN STEROID PROGESTOGEN, VED VAATGRANULERING, SAMT TABLE
☑	MX9702162A	1997-06-28	1997-03-20	PROCESS OF MAKING DOSAGE U GRANULATION.
☑	**JP10505846T2**	1998-06-09	1995-09-19	
☑	HU0077611A2	1998-06-29	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	HK1002172A1	2003-08-22	1998-02-13	PROCESS OF MAKING DOSAGE U GRANULATION
☑	FI0971172A0	1997-03-20	1997-03-20	MENETELMAE ANNOSYKSIKKOEJ VALMISTAMISEKSI MAERKAERAK
☑	FI0971172A	1997-03-20	1997-03-20	MENETELMAE ANNOSYKSIKKOEJ VALMISTAMISEKSI MAERKAERAK
☑	FI0118791B1	2008-03-31	1997-03-20	Menetelmä annosyksikköjen valmista märkärakeistamalla
☑	ES2196079T3	2003-12-16	1995-09-19	PROCEDIMIENTO DE FABRICACIO UNIDADES POSOLOGICAS POR M GRANULACION POR VIA HUMEDA
☑	EP0782449B1	2003-04-09	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	EP0782449A1	1997-07-09	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	DK0782449T3	2003-08-04	1995-09-19	FREMGANGSMAADE TIL FREMST DOSERINGSENHEDER VED VAADGRANULERING
☑	DE69530308T2	2003-10-16	1995-09-19	VERFAHREN ZUR HERSTELLUNG DOSIERUNGSFORMEN DURCH FEUCHTGRANULIERUNG
	DE69530308C0	2003-05-15	1995-09-19	VERFAHREN ZUR HERSTELLUNG DOSIERUNGSFORMEN DURCH FEUCHTGRANULIERUNG
☑	CZ9700899A3	1997-09-17	1995-09-19	PROCESS FOR PREPARING PHAR MEDICAMENTOUS FORMS
☑	CZ0289081B6	2001-10-17	1995-09-19	PROCESS FOR PREPARING PHAR MEDICAMENTOUS FORM AND TAB
☑	CN1161650A	1997-10-08	1995-09-19	PROCESS FOR MAKING DOSAGE WET GRANULATION
☑	CN1101681C	2003-02-19	1995-09-19	Process for making dosage units by w
	CN1101681B	2003-02-19		
☑	CA2200754C	2008-04-15	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	CA2200754AA	1996-03-28	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	BR9509019A	1997-12-30	1995-09-19	PROCESSO PARA FABRICAR UNID DOSAGEM FARMACEUTICA E COM ISENTO DE SOLVENTES ORGANIC
☑	AU3608295A1	1996-04-09	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	AU0700645B2	1999-01-14	1995-09-19	PROCESS OF MAKING DOSAGE U GRANULATION
☑	AT0236639E	2003-04-15	1995-09-19	VERFAHREN ZUR HERSTELLUNG DOSIERUNGSFORMEN DURCH FEUCHTGRANULIERUNG
34 family members shown above				

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Other Abstract Info:

すことにより達成され得、一方比較的多量の場合はV形ブレンダー、ダブルコーンブレンダー、遊星形混合機、回転式造粒機、高剪断混合機および流動床造粒装置が適用され得る。一般的混合法は、「ファーマスーティカル・ドウシジ・フォームズ（Ｆｈａｒｍａｃｅｕｔｉｃａｌ　Ｄｏｓａｇｅ　Ｆｏｒｍｓ）（第２巻），編者エイチ・エイ・リーベルマン、エル・ラッチマン、ジェイ・ビー・シュワルツ（１９９０），マーセル・デッカー・インク，ニューヨークおよびバーゼル，ｐｐ．１～７１」に開示されている。乾燥賦形剤および超微粉砕されたまたは微細に粉砕された活性成分は、適当な混合機中で好ましくは混合および粒状化の両方共が遂行され得る混合機例えばグラル（Ｇｒａｌ）高剪断混合機中で混合され、その後水性結合剤溶液が添加される。別の好ましい方法は、活性成分を水性結合剤溶液中に懸濁することであり、しかしてこの懸濁液が賦形剤の乾燥混合物に添加されそして粒状化される。

湿式粒状化により製造された粒状物およびタブレットは、一

般に慣用の固体状経口投与形態中に見られ得る数種の不活性物質から成る。それらの成分は、希釈剤、結合剤、滑走剤および滑沢剤のような、満足な加工および圧縮特性を処方物に付与するのを助勢する賦形剤において、並びに崩壊剤および着色剤のような、望ましい物理的特性を最終タブレットに与えるべき賦形剤において分類され得る。要求されるなら、タブレットは、例えば「ファーマスーティカル・ドウシジ・フォームズ（Ｆｈａｒｍａｃｅｕｔｉｃａｌ　Ｄｏｓａｇｅ　Ｆｏｒｍｓ）（第３巻），編者エイチ・エイ・リーベルマン、エル・ラッチマン、ジェイ・ビー・シュワルツ（１９９０），マーセル・デッカー・インク，ニューヨークおよびバーゼル，ｐｐ．９３～１２５」に開示されているように、皮膜状被膜が付与され得る。

希釈剤（充填剤）または増量剤は、通常、タブレットの大部分を構成する。最も普通に用いられる希釈剤のグループは、水不溶性のリン酸カルシウム（二塩基性および三塩基性）、硫酸カルシウム二水和物、炭酸カルシウム、デンプン、変性デンプンおよび微晶質セルロース並びに水溶性のラクトース、スクロース、デキストロース、マンニットおよびソルビットを含む。

含で製造されたタブレットよりも湿気に対してはるかに安定であるタブレットが製造され得るところのデソゲストレルまたはＯｒｇ３０６５９およびエチニルエストラジオールの粒状物をもたらす、ということが今般見出された。

湿式粒状化は、凝塊または顆粒を生成させるために水または有機溶媒が適用される点で乾式粒状化から区別される。

製薬工業において最も広範に用いられている粒状化法は、流動床粒状化法および湿式塊化法（顆粒または凝塊物をもたらす任意のタイプのかきまぜ機を備えた容器中で液体が粉末または

粒状物に添加される。）である。種々の操作が湿式（塊化）粒状化において認識され得、しかしてそれらは、薬および賦形剤の粉砕、粉砕された粉末の混合、結合剤溶液の調製、湿性塊を形成させるための該結合剤溶液と該粉末混合物との混合、湿性塊の粗選別、湿り顆粒の乾燥、乾燥顆粒の選別、選別された顆粒と滑沢剤および崩壊剤との混合および最後にこれらの粒状物のカプセルへの充填またはこれらの粒状物のタブレットへの圧縮を含む。選択される賦形剤およびバッチのサイズ並びに選択される装置に依り、該操作のいくつかは一緒にされ得または必要とされず、あるいは特別な操作が含められ得る、ということが明らかである。顆粒を製造する一般的方法は、例えば、「ファーマスーティカル・ドウシジ・フォームズ（Ｆｈａｒｍａｃｅｕｔｉｃａｌ　Ｄｏｓａｇｅ　Ｆｏｒｍｓ）：タブレッツ（Ｔａｂｌｅｔｓ）（第Ｉ巻），編者エイチ・エイ・リーベルマン、エル・ラッチマン、ジェイ・ビー・シュワルツ（１９８９），マーセル・デッカー・インク，ニューヨークおよびバーゼル，ｐｐ．１３１～１９０」に記載されている。

湿式粒状化の利点は、粉末の凝集性および圧縮性の向上、超微粉砕されたまたは微細に粉砕された低投与薬の良好な分布お

よび均一な含量、多量の塵および空気媒介汚染の低減、成分の凝離の防止を含む。

小規模の製造は乳鉢またはステンレス鋼製ボウル中で素材を混合しそして湿ら

粉末を一緒に結合しそして凝集性をタブレット処方物に与え

る物質は、結合剤または接着剤である。結合剤は、乾燥状態で添加されそして希釈剤および薬とブレンドされ得る。この場合、結合剤は、水または他の溶媒の添加により活性化される。他の製造処理操作において、接着剤が液体に溶解またはスラリー化されそしてこの形態にて混合粉末に添加される。慣用の結合剤は、ゼラチン、水溶性の変性デンプン、並びにスクロース、グルコース、デキストロース、糖蜜およびラクトースのような糖を含む。用いられてきた天然および合成のガムは、トラガカント、珪酸アルミニウムマグネシウム、アラビアゴム、アルギン酸カルシウムアンモニウム、アルギン酸ナトリウム、カルボキシメチルセルロース、ヒドロキシプロピルセルロース、メチルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、ポリエチレングリコールおよびビーガムのような粘土を含む。例えば種々の液体中の結合剤の溶解度に依り、結合剤は、水中、水－溶媒の混合物中および有機溶媒中の溶液として粉末混合物に添加され得る。

流動特性を改善するための物質は、滑走剤と称される。例として、粒子間摩擦を低減するためにおよびタブレット成形機において大きい開口から小さい開口への物質の流れと関連した問

題を除去するために、二酸化珪素、マグネシウムラウリルサルフェート、珪酸アルミニウムマグネシウム、酸化マグネシウム、タルクまたは粘土が処方物中に混入され得る。

カプセルまたはサッシェに充填する前にまたはタブレットを圧縮する前に、滑沢剤が、加工中摩擦および摩損を防ぐためにたいてい添加される。滑沢剤のいくつかはまた、パンチおよびダイ壁の各面にタブレット粒状化物が粘着する場合に関連があり得る抗付着性を示す。滑沢剤のグループの例は、金属ステアレート（マグネシウムステアレート）、タルク、ステアリン酸、ナトリウムステアリルフマレート、水素添加植物油、高溶融点ロウおよびコーンスターチである。

タブレットが崩壊しそして溶解して活性成分を放出するのを助勢するためにタ

ブレット中に混入される成分は、崩壊剤である。崩壊剤の全量は、圧縮の直前に粒状化物に添加され得、湿式粒状化過程が行われる前に粉末物質の全量に添加され得、または湿式粒状化の前に添加される一部と粒状物へ乾燥状態で添加される一部に単に分けられ得る。適用され得る崩壊剤のグループの例は、デンプン（スターチ（Ｓｔａｒｃｈ）１５００）、微晶質セルロース（アヴィセル（Ａｖｉｃｅｌ）ＰＨ１０１お

よびアヴィセル（Ａｖｉｃｅｌ）ＰＨ１０２）、精製木材セルロース、アルギン酸、ナトリウムデンプングリコレート、グアーガム、クロスカルメロースナトリウム（ｃｒｏｓｓ　ｃａｒｍｅｌｌｏｓｅ　ｓｏｄｉｕｍ）、架橋ポリビニルピロリドンおよびイオン交換樹脂である。

本発明の方法により得られるタブレットは、有機溶媒を含んでおらず、そして各製薬投与単位体の約０．００５～１．０重量パーセントの量にて存在するデソゲストレルおよびＯｒｇ３０６５９から選択されたプロゲストゲン、２０重量％未満（例えば、０．５～２０重量％）好ましくは１０重量％未満である少量の水、および随意にエストロゲンからなる。好ましくは、プロゲストゲンはデソゲストレルでありそしてエストロゲンはエチニルエストラジオールである。水の量は変動し得、そして適用される乾燥条件に左右される。しかしながら、該タブレットは、常に微量の水通常１０重量％未満好ましくは約０．５～１０重量％を有する。

本発明は、次の例により更に例示される。

例Ｉ

活性成分を加工して、次のもの（タブレット当たり）：

デソゲストレル（超微粉砕された）	１５０μｇ
ＥＥ（超微粉砕された）	３０μｇ
ヒドロキシプロピルセルロース	１．９５ｍｇ
コーンスターチ	６．５０ｍｇ
コロイド状二酸化珪素	０．９８ｍｇ

マグネシウムステアレート	０．３３ｍｇ
ラクトース	６５ｍｇまで

からなる均質粒状化物にした。

１ｋｇのバッチのために、グラル（Ｇｒａｌ）１０高剪断混合機にラクトース２００Ｍおよびコーンスターチを充填した。１分間の混合後、この塊にヒドロキシプロピルセルロースの水性粒状化用溶液（１２５ｍｌ）中のデソゲストレルおよびＥＥ（エチニルエストラジオール）の分散体を定量的に添加した。次いで２５ｍｌの水を用いてビーカーをすすぎ、そして引き続いてこれを混合物に添加した。この混合物を、該グラル（Ｇｒａｌ）１０で２．５分間粒状化した。得られた湿っている塊を、マリウス（Ｍａｒｉｕｓ）真空キャビネット中で減圧下で４０℃にて４時間乾燥した。乾燥およびエルウェカ（Ｅｒｗｅｋａ）装置での７１０μｍ篩を通じての選別後、こ

の粒状物をコロイド状二酸化珪素およびマグネシウムステアレートと混合した。この粒状物を圧縮してタブレットにした。

例ＩＩ

例Ｉにおける組成を有する粒状物を製造した。この粒状化は、結合剤溶液において水の代わりにエタノールを用いて遂行された。

例ＩＩＩ

例Ｉおよび例ＩＩからのタブレットを、それぞれ１０％および９５％の相対湿度（ＲＨ）にて２カ月間４０℃における貯蔵に付した。デソゲストレルの分解を算出した。

	分解（％）	
	１０％ＲＨ	９５％ＲＨ
タブレット例ＩＩ	1	4
タブレット例Ｉ	0	1

水性結合剤溶液を用いないで製造されたタブレットは貯蔵に関して感湿性を示す（例ＩＩ）のに対して、水性結合剤溶液を用いて製造されたタブレットはより小さい感湿性および向上された安定性を示す（例Ｉ）。

例ＩＶ

活性成分を加工して、次のもの：

Ｏｒｇ３０６５９（微細に粉砕された）	６０μｇ
ヒドロキシプロピルセルロース	１．９５ｍｇ
コーンスターチ	６．５０ｍｇ
マグネシウムステアレート	０．３２５ｍｇ
ラクトース	５６．１６５ｍｇ

からなる均質粒状化物にした。

１ｋｇのバッチのために、グラル（Ｇｒａｌ）１０高剪断混合機にラクトース２００Ｍおよびコーンスターチを充填した。１分間の混合後、この塊にヒドロキシプロピルセルロースの水性粒状化用溶液（１２５ｍｌ）中のＯｒｇ３０６５９（１７α－１７－ヒドロキシ－１１－メチレン－１９－ノルプレグナ－４，１５－ジエン－２０－イン－３－オン）の分散体を定量的に添加した。次いで２５ｍｌの水を用いてビーカーをすすぎ、

そして引き続いてこれを混合物に添加した。この混合物を、該グラル（Ｇｒａｌ）１０で２．５分間粒状化した。得られた湿っている塊を、マリウス（Ｍａｒｉｕｓ）真空キャビネット中で減圧下で４０℃にて４時間乾燥した。乾燥およびエルウェカ（Ｅｒｗｅｋａ）装置での７１０μｍ篩を通じての選別後、この粒状物をマグネシウムステアレートと混合した。この粒状物を圧縮してタブレットにした。

例Ｖ

例ＩＶにおける組成を有する粒状物を製造した。この粒状化は、結合剤溶液において水の代わりにエタノールを用いて遂行された。

例ＶＩ

例ＩＶおよび例Ｖからのタブレットを、開放ガラス容器中でそれぞれ１０％および９５％の相対湿度（ＲＨ）にて１ヵ月間３０℃における貯蔵に付した。Ｏｒｇ３０６５９の分解を算出した。

	分解（％）	
	１０％ＲＨ	９５％ＲＨ
タブレット例Ｖ	0	6
タブレット例ＩＶ	0	0

水性結合剤溶液を用いないで製造されたタブレットは貯蔵に関して感湿性を示す（例Ｖ）のに対して、水性結合剤溶液を用いて製造されたタブレットはより小さい感湿性および向上された安定性を示す（例ＩＶ）。

例ＶＩＩ

活性成分を加工して、次のもの（タブレット当たり）：

デソゲストレル（超微粉砕された）	１５０μｇ
ＥＥ（超微粉砕された）	３０μｇ
ヒドロキシプロピルセルロース	１．９５ｍｇ
コーンスターチ	６．５０ｍｇ
コロイド状二酸化珪素	０．９８ｍｇ
マグネシウムステアレート	０．３３ｍｇ
ラクトース	６５ｍｇまで

からなる均質粒状化物にした。

１ｋｇのバッチのために、グラル（Ｇｒａｌ）１０高剪断混合機にラクトース２００Ｍ、コーンスターチ、デソゲストレルおよびＥＥ（エチニルエストラジオール）を充填した。１分間の混合後、この塊にヒドロキシプロピルセルロースの水性粒状化用溶液（１２５ｍｌ）を定量的に添加した。次いで２５ｍｌの水を用いてビーカーをすすぎ、そして引き続いてこれを混合物に添加した。この混合物を、該グラル（Ｇｒａｌ）１０で２．５分間粒状化した。得られた湿っている塊を、マリウス（Ｍａｒｉｕｓ）真空キャビネット中で減圧下で４０℃にて４時間乾燥した。乾燥およびエルウェカ（Ｅｒｗｅｋａ）装置での７１０μｍ篩を通じての選別後、この粒状物をコロイド二酸化珪素およびマグネシウムステアレートと混合した。この粒状物を圧縮してタブレットにした。

例ＶＩＩＩ

例ＩＶの方法に従って、活性成分を加工して次のもの：

Ｏｒｇ３０６５９（微細に粉砕された）	６０μｇ
ポリビニルピロリドン	１．９５ｍｇ
コーンスターチ	６．５０ｍｇ
マグネシウムステアレート	０．３２５ｍｇ
ラクトース	６５ｍｇまで

からなる均質粒状化物にし、そして例ＩＶの方法により圧縮してタブレットにし

た。

例ＩＸ（比較例）

例ＶＩＩＩの組成を有する粒状物を、水の代わりにアセトンを用いて製造した。これから得られたタブレットを、開放ガラス容器中で７５％の相対湿度にて１２ヵ月間３０℃および４０℃にて貯蔵した。例ＶＩＩＩのタブレットを同じ条件下で貯蔵し、そしてゼロ時間における初期含量に対する百分率での含量を算出した。

	３０℃	４０℃
タブレット例ＶＩＩＩ	９４．４％	７３．６％
タブレット例ＩＸ	６４．１％	４４．５％

例ＸＩ

次のもの：

Ｏｒｇ３０５６９（超微粉砕された）	７．５μｇ
エストラジオール	２ｍｇ
ヒドロキシプロピルセルロース	１．９５ｍｇ
コーンスターチ	３０％
コロイド状二酸化珪素	０．９８ｍｇ
マグネシウムステアレート	０．３２５ｍｇ
ラクトース	６５ｍｇまで

からなるタブレットを製造した。

粒状化は２８０ｍｌの粒状化用液を用いて例ＩＶに従って遂行されて粒状物を得た。タブレットは、回転式プレスで圧縮された。

【国際調査報告】

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 95/03692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Boulois, D

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(54) Title: PROCESS OF MAKING DOSAGE UNITS BY WET GRANULATION

(57) Abstract

The invention relates to a process of making pharmaceutical dosage units comprising at least desogestrel or Org 30659 (17α-17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one), present in an amount of about 0.005 to 1.0 percent by weight of each pharmaceutical dosage unit, characterized in that the steroidal agent, and when required pharmaceutically acceptable excipients, are mixed with water and granulated.

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Process of making dosage units by wet granulation.

The invention relates to a process of making dosage units comprising at least desogestrel or Org 30659 (17α-17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one) present in an amount of about 0.005 to 1.0 percent by weight of each pharmaceutical dosage unit.

Methods for making tablets and other solid or dry pharmaceutical preparations are well-known. For example in the standard English language text Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture), methods of making tablets, capsules and pills and their respective components are described.

Three methods of making tablets include the wet-granulation, dry-granulation, and direct compression methods.
Wet-granulation methods involve weighing out ingredients (including a solvent), mixing the ingredients, granulating them, screening them damp, drying them, dry screening, lubrication, and compressing the resultant admixture into tablets. Such procedures result in tablets having at least adequate tablet homogeneity. Wet-granulation methods may have a disadvantage when certain solvents, which may not be desired in view of environmental and safety concerns, are used.

An additional problem occurs in providing optimal tablet homogeneity when used with certain very potent medicinal compounds. For example, compounds such as certain extremely potent steroids require only very low doses of the compound per tablet (e.g. < 1.0 milligrams (mg)/ 100 mg tablet) and do not always distribute entirely evenly

throughout a tableting mixture possibly resulting in some tablets having relatively high amounts of steroid (i.e. "superpotent tablets"), while others have very low amounts of steroid or possibly none at all.

Very few solutions for these problems are offered, among which a dry-mix procedure as disclosed in European patent application 503,521.

The present invention offers a novel solution for obtaining tablets comprising low dosage of the micronised or finely milled steroidal progestogens desogestrel or Org 30659 with excellent content uniformity, by using a wet-granulation technique, in which the progestogen, and optionally pharmaceutically acceptable excipients, are mixed with water and granulated. The granulate obtained may optionally be mixed with pharmaceutically acceptable auxiliaries, and compressed into tablets.

The method is very suitable for tablets comprising the low dosage steroidal progestogens desogestrel or Org 30569, which are present in an amount of about 0.005 to 1.0, and preferably of about 0.01 to 0.5 percent by weight of each pharmaceutical dosage unit. Under desogestrel is also to understand its active metabolite 3-keto-desogestrel.

The progestogens desogestrel and Org 30659 can be admixed with estrogens selected from ethinyl estradiol (EE), estradiol, and mestranol. Usually mixtures of progestogens and estrogens are used. Most preferred are tablets comprising desogestrel and ethinyl estradiol.

Since tablets containing desogestrel (and also tablets containing Org 30659) are known to be unstable towards moisture, many attempts are done to exclude water in the

manufacture process, for instance by using a dry-granulating method, or by using water-free organic solvents in wet-granulating methods. The marketed product (Marvelon®), for instance, is packed in a water impermeable sachet to prevent contact between the tablet and surrounding. Most remarkably it has now been found that the process of this invention, comprising granulation in an aqueous medium, provides a granulate of desogestrel or Org 30659 and ethinyl estradiol, from which tablets can be prepared which are much more stable towards moisture, than the previously aqueous-free prepared tablets.

Wet granulation distinguishes from dry granulation in that water or organic solvents are applied in wet granulation to produce agglomeration or granules.

The most widely used granulation methods in the pharmaceutical industry are the fluidized bed granulation and the wet-massing method in which a liquid is added to a powder or granulate in a vessel equipped with any type of agitation that will provide granules or agglomerates. Various operations can be recognised in the wet (massing) granulation, including milling of drugs and excipients, mixing of milled powders, preparation of binder solution, mixing the binder solution with the powder mixture to form the wet mass, coarse screening of wet mass, drying moist granules, screening dry granules, mixing the screened granules with lubricant and disintegrant, and finally filling the granulate into capsules or compressing the granulate to tablets. It is obvious that, depending on the selected excipients and the size of the batch and the selected equipment, some of the operations can be combined or are not required or particular operations can be included. General methods of preparing granules are for instance described in Pharmaceutical Dosage Forms: Tablets (Volume I). Ed.

H.A. Lieberman, L. Lachman, J.B. Schwartz (1989), Marcel Dekker Inc. New York and Basel pp. 131-190.

Advantages of wet granulation include improvement of the cohesiveness and compressibility of powders, a good distribution and uniform content of micronised or finely milled low-dosage drugs, reduction of a great deal of dust and airborne contamination, prevention of segregation of components.

Small-scale production can be achieved by mixing and wetting the mass in mortars or stainless steel bowls, whereas for larger quantities twin-shell blenders, double-cone blenders, planetary mixers, rotary granulators, high shear mixers and fluid-bed granulation equipment can be applied. General mixing methods are disclosed in Pharmaceutical Dosage Forms (Volume 2). Ed. H.A. Lieberman, L. Lachman, J.B. Schwartz (1990), Marcel Dekker Inc. New York and Basel pp. 1-71. The dry excipients and the micronised or finely milled active ingredients are mixed in a suitable mixer, preferably a mixer in which both mixing and granulating can be performed, for instance a Gral high sheer mixer, after which an aqueous binder solution is added. Another preferred method is to suspending the active ingredients into the aqueous binder solution, which suspension is added to the dry mixture of excipients and granulated.

Granulates and tablets prepared by wet-granulation consist of several inert materials that can be found in conventional solid oral dosage forms in general. The ingredients can be classified in excipients which help to impart satisfactory processing and compression characteristics to the formulation like diluents, binders, glidants and lubricants and in excipients to give the desirable physical characteristics to the finished tablet like disintegrants and colors. If

required the tablets can be provided with a film coat, for instance as disclosed in Pharmaceutical Dosage Forms (Volume 3). Ed. H.A. Lieberman, L. Lachman, J.B. Schwartz (1990), Marcel Dekker Inc. New York and Basel pp. 93-125.

Diluents (fillers) or bulking agents usually make up the major portion of the tablet. The group of most commonly used diluents include the water insoluble calcium phosphates (di- and tribasic), calcium sulfate dihydrate, calcium carbonate, starch, modified starches and microcrystalline cellulose and the water soluble lactose, sucrose, dextrose, mannitol and sorbitol.

The substances that bind powders together and provide cohesiveness to the tablet formulation are binding agents or adhesives. Binders can be added dry and blended with the diluents and the drug. In this case binders are activated by addition of water or other solvents. In other manufacturing procedures, the adhesives are dissolved or slurried in a liquid and, in this form, added to the mixed powders. Conventional binders include gelatin, water soluble modified starch, and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include tragacanth, magnesium aluminium silicate, acacia, ammonium calcium alginate, sodium alginate, carboxymethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyethylene glycol and clays like Veegum. Depending on for example the solubility of the binders in the various liquids, the binder can be added to the powder mix as a solution in water, a water-solvent mixture and in a organic solvent.

Materials to improve the flow characteristics are referred to as glidants. As an example, silicon dioxide,

magnesium lauryl sulfate, magnesium aluminium silicate, magnesium oxide, talc or clays can be incorporated into the formulation to reduce interparticulate friction and to eliminate the problems associated with the flow of materials from larger to smaller apertures in the tablet presses.

Before filling capsules or sachets, or compressing tablets, lubricants are mostly added to prevent friction and wear during processing. Some of the lubricants also demonstrate anti-adherent properties that can be relevant in case of sticking of tablet granulations to the faces of the punches and the die walls. Examples of the group of lubricants are the metallic stearates (magnesium stearate), talcum, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oil, high melting point waxes, and corn starch.

A component incorporated into the tablets to help the tablet to break up and dissolve to release the active component is the disintegrant. The total amount of disintegrant can be added to the granulation just prior to compression, can be added to the total mass of powdered materials before the wet granulation process takes place or can be simply divided into one portion added before wet granulation and one portion added dry to the granulates. Examples of the group of disintegrants that can be applied are starch (Starch 1500), microcrystalline cellulose (Avicel PH 101 and Avicel PH 102), purified wood cellulose, alginic acid, sodium starch glycolate, guar gum, cross carmellose sodium, crosslinked polyvinylpyrrolidone and ion exchange resins.

The tablets obtained by the process of this invention are free from organic solvents, and comprise a progestogen selected from desogestrel and Org 30659,

present in an amount of about 0.005 to 1.0 percent by weight of each pharmaceutical dosage unit, a small amount being less than 20% (e.g. 0.5-20%), and preferably less than 10% by weight of water, and optionally an estrogen. Preferably the progestogen is desogestrel and the estrogen is ethinyl estradiol. The amount of water can vary and depends from the drying conditions applied. The tablets, however, always possess trace amounts of water, usually less than 10 % by weight, and preferably about 0.5 to 10 % by weight.

The invention is further illustrated by the following examples.

Example I

The active ingredients were processed to a homogeneous granulation comprising (per tablet):

desogestrel (micronised)		150	µg
EE (micronised)		30	µg
hydroxypropylcellulose		1.95	mg
corn starch		6.50	mg
colloidal silicon dioxide		0.98	mg
magnesium stearate		0.33	mg
lactose	to	65	mg

For a 1 kg batch a Gral 10 high shear mixer was filled with lactose 200M and corn starch. After mixing for 1 min a dispersion of desogestrel and EE (ethinyl estradiol) in an aqueous granulation solution of hydroxypropylcellulose (125 ml) was added quantitatively to the mass. Then 25 ml of water was used to rinse the beaker and subsequently added to the mixture. The mixture was granulated with the Gral 10 for 2.5 minutes. The obtained wetted mass was dried for 4 h in a Marius vacuum cabinet under diminished pressure at 40 °C. After drying and screening through a 710 µm sieve with an

Erweka apparatus the granulate was admixed with colloidal silicon dioxide and magnesium stearate. The granulate was compressed to tablets.

Example II

A granulate with the composition in Example I was manufactured. The granulation was performed with ethanol instead of water in the binder solution.

Example III

Tablets from Example I and Example II were subjected to storage at 40 °C for two months at relative humidities (RH) of 10 and 95% respectively. The decomposition of desogestrel was calculated.

	Decomposition (%)	
	10% RH	95% RH
Tablets Example II	1	4
Tablets Example I	0	1

Tablets prepared without aqueous binder solution show susceptibility to humidity upon storage (Example II), whereas tablets prepared with an aqueous binder solution show less susceptibility to humidity and an improved stability (Example I).

Example IV

The active ingredients were processed to a homogeneous granulation comprising:

Org 30659 (finely milled)	60	µg
hydroxypropylcellulose	1.95	mg
corn starch	6.50	mg
magnesium stearate	0.325	mg
lactose	56.165	mg

For a 1 kg batch a Gral 10 high shear mixer was filled with lactose 200M and corn starch. After mixing for 1 min a dispersion of Org 30659 (17α-17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one) in an aqueous granulation solution of hydroxypropylcellulose (125 ml) was added quantitatively to the mass. Then 25 ml of water was used to rinse the beaker and subsequently added to the mixture. The mixture was granulated with the Gral 10 for 2.5 minutes.

The obtained wetted mass was dried for 4 h in a Marius vacuum cabinet under diminished pressure at 40 °C. After drying and screening through a 710 µm sieve with an Erweka apparatus the granulate was admixed with magnesium stearate. The granulate was compressed to tablets.

Example V

A granulate with the composition in Example IV was manufactured. The granulation was performed with ethanol instead of water in the binder solution.

Example VI

Tablets from Example IV and Example V were subjected to storage at 30 °C for one month at relative humidities (RH) of 10 and 95% respectively in open glass

containers. The decomposition of Org 30659 was calculated.

	Decomposition (%)	
	10% RH	95% RH
Tablets Example V	0	6
Tablets Example IV	0	0

Tablets prepared without aqueous binder solution show susceptibility to humidity upon storage (Example V), whereas tablets prepared with an aqueous binder solution show less susceptibility to humidity and an improved stability (Example IV).

Example VII

The active ingredients were processed to a homogeneous granulation comprising (per tablet):

desogestrel (micronised)		150	µg
EE (micronised)		30	µg
hydroxypropylcellulose		1.95	mg
corn starch		6.50	mg
colloidal silicon dioxide		0.98	mg
magnesium stearate		0.33	mg
lactose	to	65	mg

For a 1 kg batch a Gral 10 high shear mixer was filled with lactose 200M, corn starch, desogestrel and EE (ethinyl estradiol). After mixing for 1 min an aqueous granulation solution of hydroxypropylcellulose (125 ml) was added quantitatively to the mass. Then 25 ml of water was used to rinse the beaker and subsequently added to the mixture. The mixture was granulated with the Gral 10 for 2.5 minutes.

The obtained wetted mass was dried for 4 h in a Marius vacuum cabinet under diminished pressure at 40 °C. After drying and screening through a 710 µm sieve with an Erweka apparatus the granulate was admixed with colloidal silicon dioxide and magnesium stearate. The granulate was compressed to tablets.

Example VIII

The active ingredients were processed to a homogeneous granulation comprising:

Org 30659 (finely milled)		60	µg
polyvinylpyrrolidone		1.95	mg
corn starch		6.50	mg
magnesium stearate		0.325	mg
lactose	to	65	mg

and granulated and compresses into tablets according to the method of Example IV.

Example IX (comparison example)

A granulate having the composition of Example VIII was manufactured using acetone instead of water. The tablets obtained therefrom were stored for 12 months at 75% relative humidity at 30 °C and 40 °C in open glass containers. The tablets of Example VIII were stored under the same conditions and the content in percentage of the initial content at zero time was calculated:

	30 °C	40 °C
Tablets Example VIII	94.4 %	73.6 %
Tablets Example IX	64.1 %	44.5 %

Example XI

Tablets were prepared comprising:

Org 30569 (micronised)		7.5	µg
estradiol		2	mg
hydroxypropylcellulose		1.95	mg
corn starch		30	%
colloidal silicon dioxide		0.98	mg
magnesium stearate		0.325	mg
lactose	to	65	mg

Granulation was performed according to Example IV using 280 ml of granulation liquid to obtain granulates. Tablets were compressed on a rotary press.

Claims:

1. A process of making pharmaceutical dosage units comprising at least one steroidal progestogen selected from desogestrel and Org 30659, present in an amount of about 0.005 to 1.0 percent by weight of each pharmaceutical dosage unit, characterized in that the progestogen, and optionally pharmaceutically acceptable excipients, are mixed with water and granulated.

2. The process according to claim 1, wherein the granulate, optionally mixed with pharmaceutically acceptable auxiliaries, is compressed into tablets.

3. The process according to claim 1 or 2, wherein the progestogen is present in an amount of about 0.01 to 0.5 percent by weight of each pharmaceutical dosage unit.

4. The process according to any one of claims 1-3, wherein the progestogen is admixed with an estrogen.

5. The process according to any one of claims 1-4, wherein the progestogen is desogestrel, or wherein desogestrel is admixed with ethinyl estradiol.

6. A tablet free from organic solvents, comprising a progestogen selected from desogestrel and Org 30659, present in an amount of about 0.005 to 1.0 percent by weight of each pharmaceutical dosage unit, a small amount being less than 20% by weight of water, and optionally an estrogen.

7. The tablet of claim 6 wherein the progestogen is desogestrel and the estrogen is ethinyl estradiol.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 95/03692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DRUG DEV. AND IND. PHARMACY, vol. 7, no. 4, 1981 NEW YORK, pages 439-451, EL-SHATTAWY H.H. 'MICROMIXING OF ORAL CONTRACEPTIVES' see page 442 - page 444 ---	1-7
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P,X	& WO,A,95 17168 (APPLIED ANALYTICAL INDUSTRIES INC) 29 June 1995 see the whole document --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Boulois, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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